(7)

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321 32Y 332 351 352 360
362 36Y 386 388 43X
502 509 50Y 620 621 623
633 635 650 652 671 681
708 761 763 802 80Y AA
LP LW ML TP
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(58) Field of search
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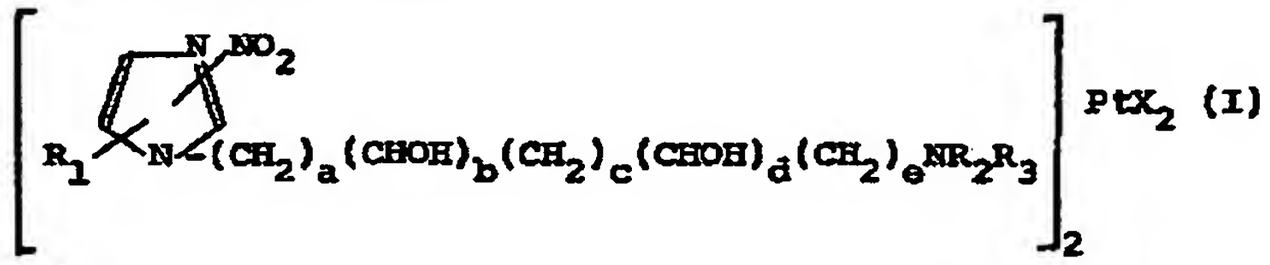
(54) Bis(nitro-1-imidazolyl alkylamine) platinum complexes useful in radiotherapy or chemotherapy

(57) Compounds of formula (I):



in which:—

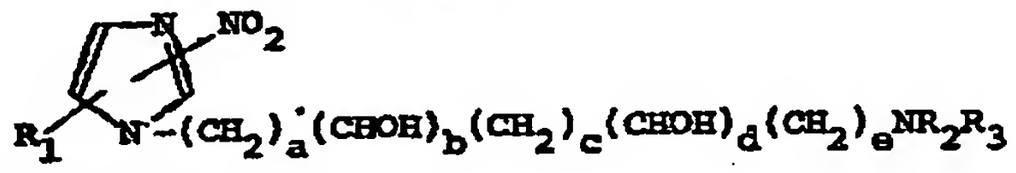
R_1 represents a hydrogen or C_1—C_6 alkyl,

R_2 and R_3 each independently represent hydrogen or C_1—C_6 alkyl,

X represents a pharmaceutically acceptable ligand incapable of co-ordinating to platinum more strongly than does nitrogen of the moiety —NR_2R_3,

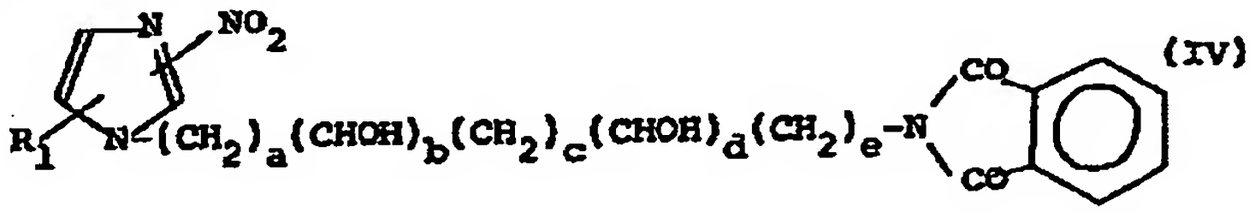
a is 1 or 2, b is 0, 1 or 2, c is 1 or 2, d is 0, 1 or 2, e is 0, 1 or 2 provided that b+d is no greater than 2 and when d is greater than 0, e is greater than 0; are useful in increasing the sensitivity of tumor cells to radiation in radiotherapy and also in potentiating or enhancing damage to tumors by chemotherapeutic agents.

Intermediates of the formulae



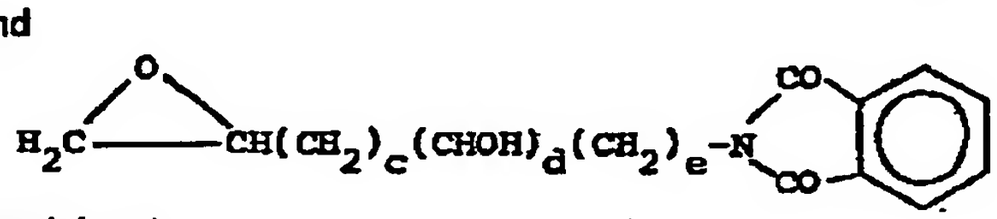
(II)

in which R_2=R_3=H,



(IV)

and



(VI)

are also claimed.

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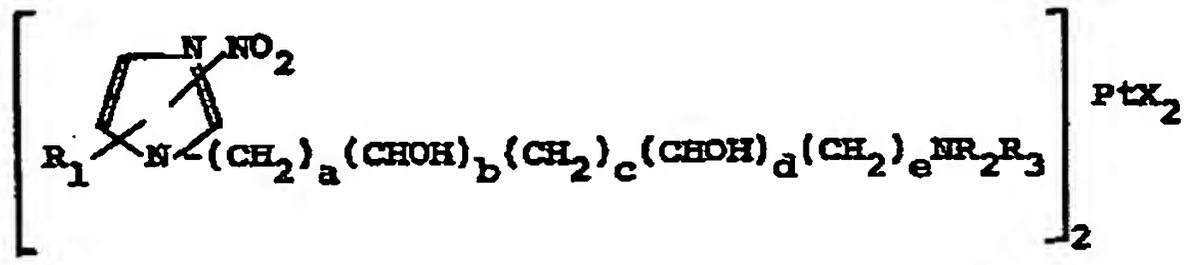
SPECIFICATION

Improvements relating to compounds useful in radiotherapy or chemotherapy

This invention relates to compounds useful in the treatment of cancer patients by radiotherapy or chemotherapy, to a process for the production of such compounds, to formulations for administration and to methods of treating such patients.

Accordingly, the present invention comprises a compound of formula I



in which:—

R_1 represents hydrogen, C_1—C_5 alkyl,

R_2 and R_3 represent hydrogen or C_1—C_6 alkyl,

X represents a pharmaceutically acceptable ligand incapable of co-ordinating to platinum more strongly than does nitrogen of the molety —NR_2R_3

a is 1 or 2

b is 0—2

c is 1 or 2

d is 0—2

e is 0—2;

provided that b+d are no greater than 2 and when d is greater than 0, e is greater than 0.

Pharmaceutically acceptable ligands X may be monodentate or form part of a bidentate ligand X_2. Although X preferably represents halogen and especially chlorine, the compound I may alternatively comprise a bidentate ligand of the formula —O.CO.CR_aR_bCO.O—, for example, in which formula R_a and R_b, which may be identical or different, each represent hydrogen or an alkyl, aryl, aralkyl, alkenyl, cycloalkyl or cycloalkenyl group or CR_aR_b represents a cycloalkyl or cycloalkenyl group. Monodentate ligands X may be identical or different.

Although when X_2 represents a bidentate ligand the configuration of the complex is necessarily *cis*, this configuration is preferred when X_2 represents two monodentate ligands.

R_1, when other than hydrogen, is typically a methyl or isopropyl group. Substituents R_1 are typically located at the ring 4 or 5 position and the nitro group is preferably located at the 2 position in the imidazole ring.

R_2 and R_3 both typically represent hydrogen although compounds in which one or both of R_2 and R_3 represent an alkyl group are also of interest.

It is generally preferred that the side chain comprises no more than five carbons so that a+b+c+d+e≯5. The presence of an hydroxyl group on the beta carbon with respect to the imidazole ring is also generally preferred, in which case when b is 1 or 2, a is usually 1. Side chains of particular interest include the following, (Im represents the imidazole ring):—

Im—$CH_2CH_2NH_2$ (a=1, b=0, c=1, d=0, e=0);

Im—$CH_2CHOHCH_2NH_2$

(a=1, b=1, c=1, d=0, e=0); Im—$CH_2CHOH(CH_2)_2NH_2$

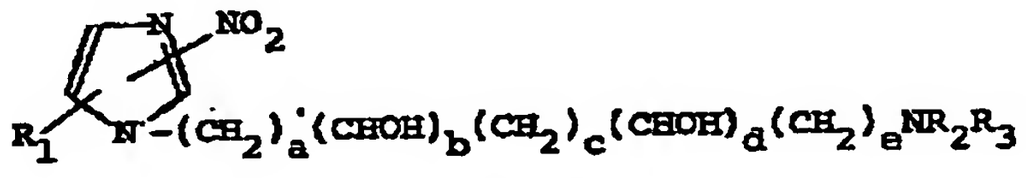
(a=1, b=1, c=2, d=0, e=0); Im—$CH_2CHOH(CH_2)_3NH_2$

(a=1, b=1, c=2, d=0, e=1); Im—$(CH_2)_2CHOH\ CH_2NH_2$

(a=2, b=1, c=2, d=0, e=0); Im—$CH_2CHOHCHOH\ CH_2NH_2$

(a=1, b=1, c=0, d=1, e=1).

Compounds I may be produced, in accordance with a further aspect of the present invention by reaction of a compound of formula II preferably in the form of an acid addition salt e.g. a hydrochloride, with a platinum compound of formula III:—



II

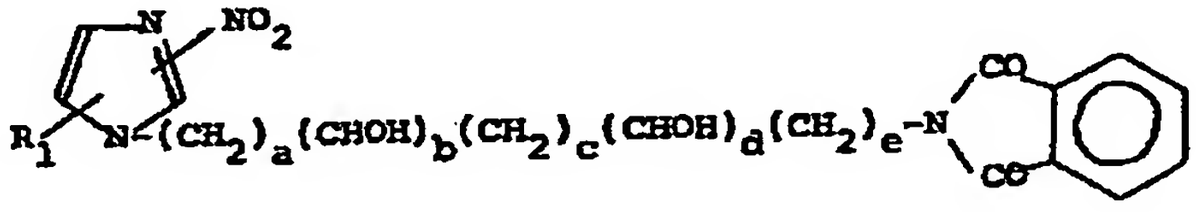
M_2PtX_4 III

wherein M represents an alkali metal e.g. potassium, X typically represents chlorine.

When the compound II is in the form of an acid addition salt, the reaction is usually conducted in the presence of a base such as sodium hydroxide so that the free amine is liberated for reaction with the compound III.

Intermediate compounds II are also included within the scope of the present invention, provided that R_2 and R_3 both represent hydrogen.

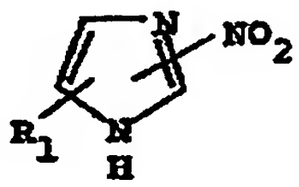
Compounds of formula II, particularly those in which R_2 and R_3 both represent hydrogen, may be prepared in accordance with a further aspect of the present invention by treatment of a phthalimide compound of formula IV with hydrazine, typically in hydrated form, suitably in a protic solvent such as an alcohol.



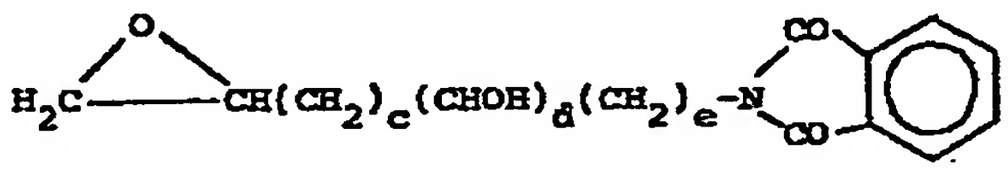
IV

Intermediate compounds of formula II wherein one or both of R_2 and R_3 represent alkyl groups may however be produced by following a method described in UK Patent Application No. 2003154A.

Intermediate compounds IV are also included within the scope of the present invention and may be prepared, in accordance with a yet further aspect of the present invention, by reaction of a nitroimidazole of formula V with a compound of formula VI:—



V

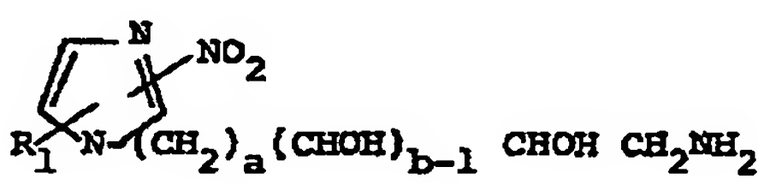


VI

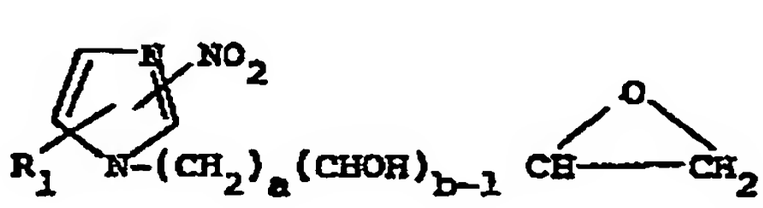
The reaction is usually conducted under basic conditions, in the presence for example of potassium carbonate and in a protic solvent, e.g. an alcohol.

Intermediate compounds VI are also included within the scope of the present invention.

Certain compounds IIA of formula II may also be produced in accordance with a further aspect of the present invention by reaction of a compound of formula VII with ammonia, preferably in aqueous solution:—



IIA



VII

Such compounds IIA may, of course, be readily converted into acid addition salts thereof by treatment with acids.

Compounds I are useful in increasing the sensitivity of tumour cells to radiation in radiotherapy and also in potentiating or enhancing damage to tumours by chemotherapeutic agents.

The compounds may be formulated in a manner appropriate to the treatment for which they are to be used by bringing them into association with pharmaceutically compatible carriers or diluents. The compounds may be included in a dosage form such as a tablet or capsule, for example a capsule comprising known formulation components such as one or more of those described in Example A of UK Patent Application No. 2003154A. The compound may also be formulated for intravenous administration e.g. in a saline drip solution.

When employed as a radiation sensitizing agent, in accordance with a further aspect of the present invention, a compound I is administered to a patient having a radiation sensitive cancer prior to irradiation of said cancer.

A compound I may, however, in a yet further aspect of the present invention be employed for chemopotentiation of a chemotherapeutic agent by administration of the compound to a patient having a localised or metastatic cancer. Administration of a compound I is generally carried out prior to or

simultaneously with administration of the chemotherapeutic agent, for example melphlan, cyclophosphamide or 5-fluorouracil or CCNU (1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea).

The invention is illustrated by the following Examples:—

Example 1

Dichloro-bis[2-(2-nitro-1-imidazolyl)ethylamine] platinum II

415 mg (1 mmol) potassium tetrachloroplatinate (II) is dissolved in 20 ml of water, filtered and added to a solution of 312 mg (2 mmol) of 2-(2-nitro-1-imidazolyl)ethylamine. The mixture is stirred at room temperature for 6 hours and a yellow solid precipitates. This precipitate is filtered, washed sequentially with water, methanol and ether and then dried at room temperature in vacuo for 10—20 hours to give the product, yield 417 mg (72%).

Example 2

Dichloro-bis[3-(2-nitro-1-imidazolyl)-2-hydroxypropylamine] platinum (II)

(a_1) N-[3-(2-Nitro-1-imidazolyl)-2-hydroxypropyl]phthalimide

A mixture of 3.39 g (30 mmol) of 2-nitroimidazole, 6.70 g (33 mmol) of N-(2,3-epoxypropyl)phthalimide, 0.50 g of anhydrous potassium carbonate and 100 ml of ethanol is heated under reflux for 5—6 hours. After 1—2 hours a new, crystalline solid begins to form. The hot mixture is filtered and the solid is washed with water, boiling ethanol and dried to yield 5.61 g (59%) of N-[3-(2-nitro-1-imidazolyl)-2-hydroxypropyl]phthalimide as a yellow coloured crystalline solid, m.p. 212—214°C.

(a_2) N-[3-(2-Nitro-1-imidazolyl)-2-hydroxypropyl]phthalimide

(Alternative method)

A mixture of 5.10 g (30 mmol) 1-(2,3-epoxypropyl)-2-nitroimidazole, 4.41 g (30 mmol) phthalimide, 0.50 g anhydrous potassium carbonate and 100 ml ethanol is heated under reflux for 4—16 hours. During refluxing a new, crystalline solid begins to form. The hot mixture is filtered and the solid is washed sequentially with water, and boiling ethanol and dried to give 5.89 g (62%) of N-[3-(2-nitro-1-imidazolyl)-2-hydroxypropyl]phthalimide as a yellow coloured crystalline solid m.p. 212—214°C.

(b) 3-(2-Nitro-1-imidazolyl)-2-hydroxypropylamine hydrochloride

A mixture of 15.08 g (50 mmol) N-[3-(2-nitro-1-imidazole)-2-hydropropyl]phthalimide, 2.76 g (55 mmol) hydrazine hydrate (99—100%) and 200 ml ethanol is heated under reflux for 1—2 hours. After cooling, 50 ml of water is added and ethanol is removed by concentration under reduced pressure. The mixture is warmed to 50°C for 1 hour with 100 ml of 5NHCl and allowed to cool to room temperature over 30 minutes. The phthalhydrazide is removed by filtration. The filtrate is concentrated under reduced pressure and the residue is redissolved in the minimum quantity of hot water, treated with decolourising charcoal, filtered and allowed to crystallise to yield 7.83 g (70%) 3-(2-nitro-1-imidazolyl)-2-hydroxypropylamine hydrochloride in the form of a white coloured crystalline solid melting point 211—213°C.

(c) Dichloro-bis[3-(2-nitro-1-imidazolyl)-2-hydroxypropylamine] platinum (II)

415 mg (1 mmol) K_2PtCl_4 and 4.46 mg (2 mmol) 3-(2-nitro-1-imidazolyl)-2-hydroxypropylamine hydrochloride are dissolved in the minimum amount of water, filtered and IN NaOH (2 ml) is added to the solution which is stirred at room temperature for 4—20 hours when a yellow precipitate forms. Further material is obtained on allowing the filtrate to stand. The product is filtered off, washed sequentially with water, methanol and ether and dried at room temperature in vacuum for 10—20 hours to yield 5.08 mg (79%) product.

Example 3

Dichloro-bis[4-(2-nitro-1-imidazolyl]-3-hydroxybutylamine] platinum (II)

(a) N-(3-butenyl)phthalimide

A mixture of 37.0 g (0.2 mol) potassium phthalimide, 29.80 g (0.22 mol) 4-bromo-1-butene and 150 ml N,N-dimethylformamide is heated at 100—120°C for 1.5 hours. The precipitated potassium bromide is filtered off, and the excess 4-bromo-1-butene and N,N-dimethylformamide are removed under reduced pressure. The residue is taken up in chloroform/water and chloroform extract is washed sequentially with 0.1N sodium hydroxide, water and then dried. Filtration and concentration gives a yellow-brown oil which is extracted with hot petroleum ether b.p. 60—80°C and the insoluble material is removed. The resultant solution is concentrated and, from this, 23 g (57%) N-(3-butenyl)phthalimide, is obtained as a white crystalline solid m.p. 50—52°C.

(b) N-(3,4-Epoxybutyl)phthalimide

To a solution of 20.10 g (0.10 mol) N-(3-butenyl)phthalimide and 0.50 g 3-*tert*-butyl-4-hydroxy-5-methylphenyl sulphide in 200 ml 1,2-dichloroethane is added 22.36 g (0.13 mol) *m*-chloroperoxybenzoic acid in 100 ml 1,2-dichloroethane during a period of 4 hours at 0°C. After the

addition the reaction mixture is stirred at room temperature for 10—20 hours and then refluxed for 2 hours. The mixture is washed sequentially with saturated sodium bicarbonate solution, 10% sodium carbonate solution, water and then dried. The 1,2-dichloroethane was removed under reduced pressure and the resulting residue is crystallised from ether/petroleum ether to give 17.06 g (79%) N-(3,4-epoxybutyl)phthalimide in the form of a white solid m.p. 83—85°C.

(c) N-[4-(2-Nitro-1-imidazolyl)-3-hydroxybutyl]phthalimide

In a manner analogous to that described in Example 2(a_1) there is obtained by reaction of the product from the latter procedure (b) N-[4-(2-nitro-1-imidazolyl)-3-hydroxybutyl]phthalimide in the form of a yellow coloured solid of melting point 220—222°C; yield (64%).

(d) 4-(2-Nitro-1-imidazolyl)-3-hydroxybutylamine hydrochloride monohydrate

In a manner analogous to that described in Example 2(b) there is obtained by reaction of the product from the latter procedure (c), after crystallisation from water/ethanol, 4-(2-nitro-1-imidazolyl)-3-hydroxybutylamine hydrochloride in the form of a white crystalline solid of melting point 184—186°C; yield (78%).

(e) Dichloro-bis[4-(2-nitro-1-imidazolyl)-3-hydroxybutylamine] platinum (II).

In a manner analogous to that described in Example 2(c) there is obtained by reaction of the product from the latter procedure (d) dichloro-bis[4-(2-nitro-1-imidazolyl)-3-hydroxybutylamine] platinum (II) in the form of a yellow crystalline solid, yield 586 mg (88%).

Example 4

Dichloro-bis[5-(2-nitro-1-imidazolyl)-4-hydroxypentylamine] platinum (II)

(a) N-(4-Pentenyl)phthalimide

In a manner analogous to that described in Example 3(a) there is obtained from 5-bromo-1-pentene after crystallisation from petroleum ether b.p. 60—80°C, N-(4-pentenyl)phthalimide in the form of a white crystalline solid, melting point 35—37°C, yield 29.04 g (67%).

(b) N-(4,5-Epoxypentyl)phthalimide

In a manner analogous to that described in Example 3(b) there is obtained from the product of the latter procedure (a) after crystallisation from ether/petroleum ether b.p. 60—80°C at a low temperature, N-(4,5-epoxypentyl)phthalimide in the form of a colourless oil (at room temperature), yield 75%.

(c) N-[5-(2-Nitro-1-imidazolyl)-4-hydroxypentyl]phthalimide

3.39 g (30 mmol) 2-nitroimidazole are heated with 6.93 g (30 mmol) N-(4,5-epoxypentyl)phthalimide and 0.50 g anhydrous potassium carbonate in 100 ml of ethanol for 6 hours. The potassium carbonate is removed by filtration and the filtrate is concentrated and allowed to cool to give N-[5-(2-nitro-1-imidazolyl)-4-hydroxypentyl]phthalimide which is recrystallised from ethanol as a yellow crystalline solid, melting point 150—152°C; yield 5.78 g (56%).

(d) 5-(2-Nitro-1-imidazolyl)-4-hydroxypentylamine hydrochloride monohydrate

In a manner analogous to that described in Example 2(b) there is obtained, from the product of the latter procedure (c) after crystallisation from aqueous ethanol 90%, 5-(2-nitro-1-imidazolyl)-4-hydroxypentylamine hydrochloride in the form of a white crystalline solid, melting point 146—147°C; yield 74%.

(e) Dichloro-bis[5-(2-nitro-1-imidazolyl)-4-hydroxypentylamine] platinum (II)

In a manner analogous to that described in Example 2(c) there is obtained from the product of the latter procedure (d) dichloro-bis[5-(2-nitro-1-imidazolyl)-4-hydroxypentylamine] platinum (II) in the form of a brown sticky solid which changes to a yellow coloured solid on drying and grinding; yield 584 mg (80%).

Example 5

Dichloro-bis[4-(2-nitro-1-imidazolyl)-2-hydroxybutylamine] platinum (II)

(a) 1-(2-Nitro-1-imidazolyl)-3-butene

A mixture of 11.3 g (0.10 mol) 2-nitroimidazole, 5.4 g (0.10 mol) sodium methoxide, 0.200 g sodium iodide, 13.5 g (0.10 mol) 4-bromo-1-butene, 100 ml N,N-dimethylformamide and 50 ml methanol is heated at 110—112°C for 4 hours. The reaction mixture is raised to the required temperature by allowing the methanol to evaporate. The precipitated sodium bromide is filtered off and the solvents are removed under reduced pressure to give a brown oil, which is taken up in chloroform/1N sodium hydroxide. The chloroform extract is washed with water, dried, filtered and concentrated to give a brown oily residue, from which 13.36 g (80%) 1-(2-nitro-1-imidazolyl)-3-butene is obtained in the form of a yellow coloured oil after carrying out column chromotography using silica gel as adsorbent.

(b) 1-(2-Nitro-1-imidazolyl)-3,4-epoxybutane

In a manner analogous to that described in Example 3(b) there is obtained, from the product of the latter procedure (a) after column chromatography through silica gel column, 1-(2-nitro-1-imidazolyl)-3,4-epoxybutane in the form of a yellow coloured oil; yield 88%.

(c) N-[4-(2-Nitro-1-imidazolyl)-2-hydroxybutyl]phthalimide

In a manner analogous to that described in Example 2(a_2) there is obtained N-[4-(2-nitro-1-imidazolyl)-2-hydroxybutyl]phthalimide in the form of a yellow crystalline solid, melting point 189—191°C; yield (57%).

(d) 4-(2-Nitro-1-imidazolyl)-2-hydroxybutylamine hydrochloride

In a manner analogous to that described in Example 2(b) there is obtained 4-(2-nitro-1-imidazolyl)-2-hydroxybutylamine hydrochloride in the form of a pale yellow gum which is homogeneous; thin-layer chromatography indicates the yield is 78%.

(e) Dichloro-bis[4-(2-nitro-1-imidazolyl)-2-hydroxybutylamine] platinum (II)

In a manner analogous to that described in Example 2(c) there is obtained dichloro-bis[4-(2-nitro-1-imidazolyl)-2-hydroxybutylamine] platinum (II) in the form of a yellow crystalline solid, yield 68%.

Example 6

Dichloro-bis[4-(2-nitro-1-imidazolyl)-2,3-dihydroxybutylamine] platinum (II)

Method A

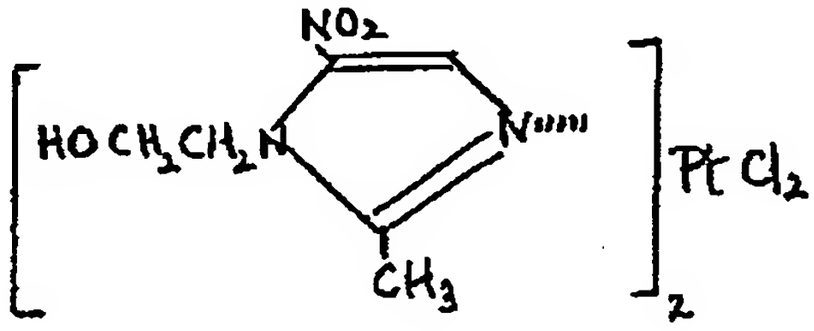
Phthalimide is treated with a mixture of 3,4 epoxy but-1-ene, ethanol and potassium carbonate to yield N-(2-hydroxy-3-butenyl)phthalimide which is treated with *m*-chloroperbenzoic acid in dichloroethane to yield N-(2-hydroxy-3,4 epoxybutyl)phthalimide. The latter compound is treated with a mixture of ethanol and potassium carbonate to yield 4-(2-nitro-1-imidazolyl)-2,3-dihydroxybutyl phthalimide which on treatment with a mixture of hydrazine and 4N hydrochloric acid gives 3-(2-nitro-1-imidazolyl)-2,3-dihydroxybutylamine hydrochloride. Reaction of the latter compound with potassium chloroplatinate yields the platinum complex.

Method B

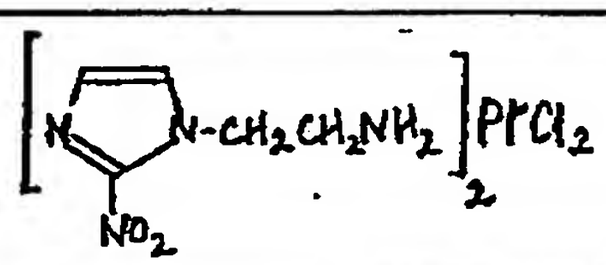
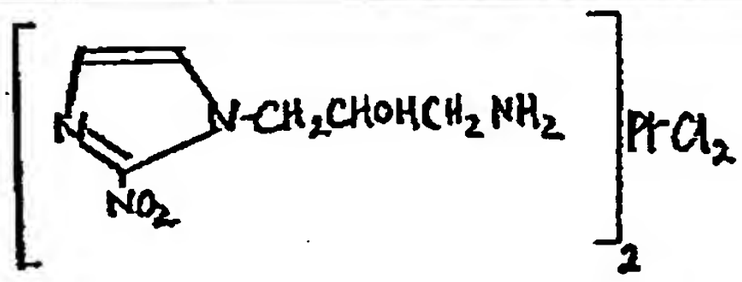
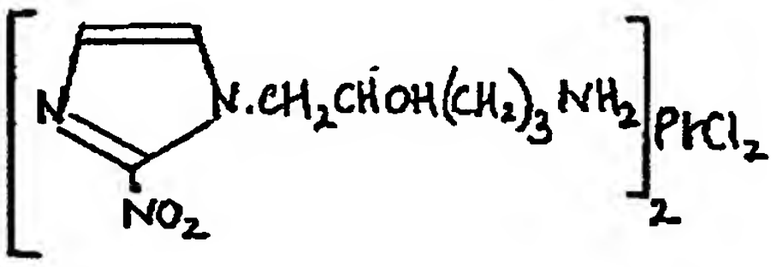
2-Nitroimidazole is reacted with a mixture of 3,4-epoxybut-1-ene ethanol and potassium carbonate to yield 1-(2-nitroimidazolyl)-2-hydroxy-3-butene, which on oxidation by *m*-chloroperbenzoic acid in dichloroethane, yields 1-(2-nitroimidazolyl)-2-hydroxy-3,4-epoxybutane. The latter compounds on reaction with a mixture of phthalimide, ethanol and potassium carbonate yields 4-(2-nitroimidazolyl)-2,3-dihydroxybutyl phthalimide which is converted to the required platinum complex by following Method A.

Examples 7—9

The following Examples illustrate the enhancement ratios obtained by the use of the compounds of Examples 1, 2 and 4 prior to irradiation of hypoxic U79 cells. The results are set out in the Table together with comparison results using the complex 'FLAP'.



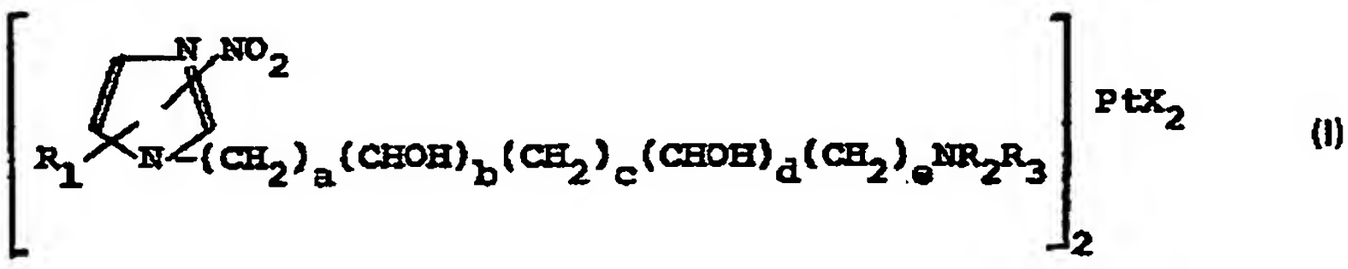
Table

Ex No.	Structure	Enhancement ratio at 0.1 mM dosage	Enhancement ratio at maximum conc tested
1		1.67	2.13[a]
2		1.36	1.53[b]
4		1.30	1.41[b]
Comparison	FLAP	1.10	1.16[b]

[a]: Toxic concentration of 0.25 mM (survival level 40% of control)
[b]: 0.25 mM non-toxic concentration

Claims

1. A compound of formula (I)



(I)

in which:—

R_1 represents hydrogen or C_1—C_6 alkyl,

R_2 and R_3 each independently represent hydrogen or C_1—C_6 alkyl,

X represents a pharmaceutically acceptable ligand incapable of co-ordinating to platinum more strongly than does nitrogen of the moiety —NR_2R_3

a is 1 or 2
b is 0, 1 or 2
c is 1 or 2
d is 0, 1 or 2
e is 0, 1 or 2

provided that b+d is no greater than 2 and when d is greater than 0, e is greater than 0.

2. A compound according to claim 1 in which the pharmaceutical acceptable ligands X are identical or different monodentate ligands.

3. A compound according claim 2 in which both ligands X represent halogen.

4. A compound according to claim 3 in which both ligands X represent chlorine.

5. A compound according to any one of claims 2 to 4 which has a *cis* configuration.

6. A compound according to claim 1 in which X_2 represent a bidentate ligand.

7. A compound according to claim 6 in which the bidentate ligand has the formula —O.CO.CR_aR_bCO.O—, in which R_a and R_b, which may be identical or different, each represent hydrogen or an alkyl, aryl, aralkyl, alkenyl, cycloalkyl or cycloalkenyl group or CR_aR_b represents a cycloalkyl or cycloalkenyl group.

8. A compound according to any one of the preceding claims in which R_1 is a methyl or isopropyl group.

9. A compound according to any one of the preceding claims in which R_1 is located at the 4- or 5-position and the nitro group is located at the 2-position in the imidazole ring.

10. A compound according to any one of the preceding claims in which R_2 and R_3 both represent hydrogen.

11. A compound according to any one of the preceding claims in which a+b+c+d+e≥5.

12. A compound according to any one of the preceding claims in which b is 1 or 2 and a is 1.

13. Dichloro-bis[2-(2-nitro-1-imidazolyl)ethylamine] platinum II.

14. Dichloro-bis[3-(2-nitro-1-imidazolyl)-2-hydroxypropylamine] platinum II.

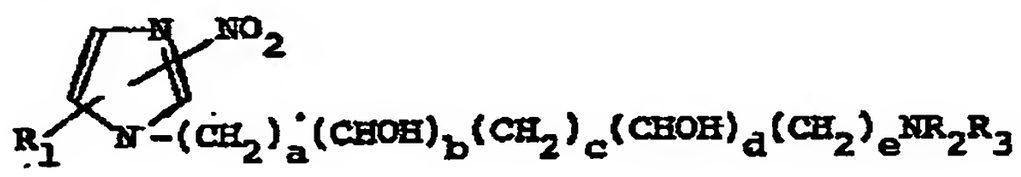
15. Dichloro-bis[4-(2-nitro-1-imidazolyl)-3-hydroxybutylamine] platinum II.

16. Dichloro-bis[5-(2-nitro-1-imidazolyl)-4-hydroxypentylamine] platinum II.

17. Dichloro-bis[4-(2-nitro-1-imidazolyl)-2-hydroxybutylamine] platinum II.

18. Dichloro-bis[4-(2-nitro-1-imidazolyl)-2,3-dihydroxybutylamine] platinum II.

19. A process for the preparation of a compound of formula (I) as defined in claim 1, which process comprises reacting a compound of formula (II)



(II)

in which R_1, R_2, R_3, a, b, c, d and e are as defined in claim 1, or an acid addition salt thereof, with a platinum compound of formula (III):

$$M_2PtX_4 \qquad \text{(III)}$$

wherein M represents an alkali metal and X is as defined in claim 1.

20. A process according to claim 19 in which the compound of formula (II) is in the form of its hydrochloride.

21. A process for the preparation of a compound of formula (I) as defined in claim 1, said process being substantially as hereinbefore described in any one of Examples 1 to 6.

22. A formulation comprising a compound of formula (I) as defined in claim 1 in association with a pharmaceutically acceptable carrier or diluent.

23. A method of increasing the sensitivity to radiation of tumor cells of a patient having a radiation-sensitive cancer, which method comprises administering to the patient a compound of formula (I) as defined in claim 1 prior to irradiation of said cancer.

24. Products containing a compound of formula (I) as defined in claim 1 and a chemotherapeutic agent as a combined preparation for simultaneous or separate use or for sequential use in which the compound of formula (I) is administered prior to the chemotherapeutic agent in the treatment of a localised or metastatic cancer.

25. Products according to claim 24 in which the chemotherapeutic agent is melphlan, cyclophosphamide, 5-fluorouracil or 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea.

26. A compound of formula (II) as defined in claim 19 in which both R_2 and R_3 represent hydrogen and acid addition salts thereof.

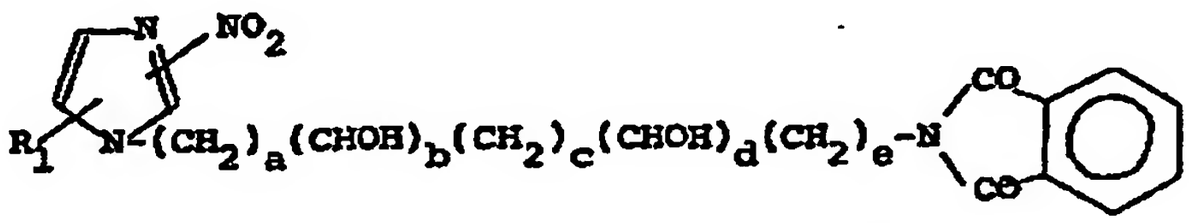
27. 2-(2-Nitro-1-imidazolyl)ethylamine

28. 3-(2-Nitro-1-imidazolyl)-2-hydroxypropylamine hydrochloride.

29. 4-(2-Nitro-1-imidazolyl)-3-hydroxybutylamine hydrochloride monohydrate.

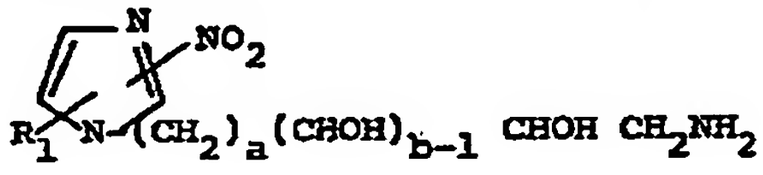
30. 5-(2-Nitro-1-imidazolyl)-4-hydroxypentylamine hydrochloride monohydrate.

31. 4-(2-Nitro-1-imidazolyl)-2-hydroxybutylamine hydrochloride.
32. 3-(2-Nitro-1-imidazolyl)-2,3-dihydroxybutylamine hydrochloride.
33. A process for the preparation of a compound of formula (II) as defined in claim 17 in which R_2 and R_3 both represent hydrogen, or an acid addition salt thereof, which process comprises of treating a phthalimide of formula (IV)



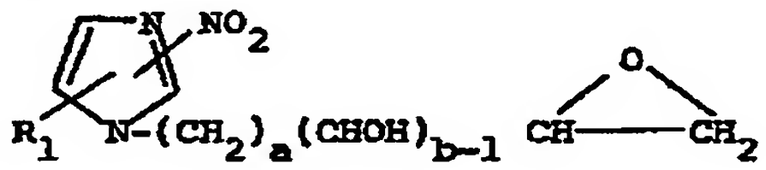
(IV)

in which R_1, a, b, c, d and e are as defined in claim 1, with hydrazine and if desired, converting the resulting compound of formula (II) into an acid addition salt thereof.
34. A process for the preparation of a compound of formula (IIA):



(IIA)

in which R_1, a and b are as defined in claim 1, or an acid addition salt thereof, which process comprises reacting a compound of formula (VII):

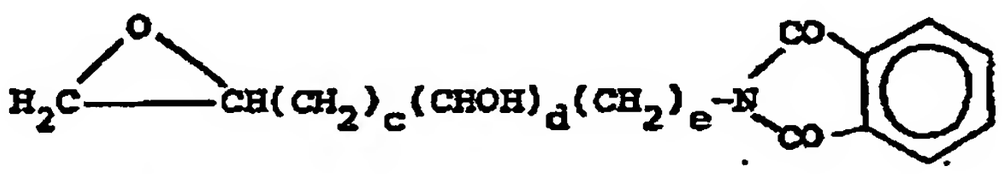


(VII)

in which R_1, a and b are as defined in claim 1, with ammonia.
35. A process for the preparation of a compound of formula (II) as defined in claim 19 in which R_2 and R_3 both represent hydrogen or an acid addition salt thereof, said process being substantially as hereinbefore described in any one of Examples 2 to 6.
36. A compound of formula (IV) as defined in claim 33.
37. N-[3-(2-Nitro-1-imidazolyl)-2-hydroxypropyl]phthalimide.
38. N-[4-(2-Nitro-1-imidazolyl)-3-hydroxybutyl]phthalimide.
39. N-[5-(2-Nitro-1-imidazolyl)-4-hydroxypentyl]phthalimide.
40. N-[4-(2-Nitro-1-imidazolyl)-2-hydroxybutyl]phthalimide.
41. 4-(2-Nitroimidazolyl)-2,3-dihydroxybutyl phthalimide.
42. A process for the preparation of a compound of formula (IV) as defined in claim 33 in which b is 1, which process comprises reacting a nitroimidazole of formula (V):

(V)

with the compound of formula (VI):



(VI)

in which c, d and e are as defined in claim 1.
43. A process for the preparation of a compound of formula (IV) as defined in claim 33 in which b is 1, said process being substantially as hereinbefore described in any one of Examples 2 to 6.
44. A compound of formula (VI) as defined in claim 18.
45. N-(2,3-Epoxypropyl)phthalimide.
46. N-(3,4-Epoxybutyl)phthalimide.
47. N-(4,5-Epoxypentyl)phthalimide.
48. N-(2-Hydroxy-3,4-epoxybutyl)phthalimide.

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